

REMARKS

Claims 1-21, 24 and 25 are canceled and claims 21-23 amended. Upon entry of the amendment, claim 21-23 will be pending. Support for the amendments can be found, for example, in Example 1.

Objections

Sequence Compliance

The Examiner has objected to the Sequence Listing as failing to include the two sequences listed on page 1. The specification has been amended to delete paragraph 4 of page 1 which contained the 2 sequences. It is submitted that the originally submitted Sequence Listing is in compliance with the sequence listing requirements.

Specification

The Examiner has objected to the specification, as the status of the priority applications is not cited. Applicant submits that, as all of the priority applications are provisional applications, citation of their status is not required. (MPEP 201.11).

Rejections

Rejections under 35 U.S.C. §§ 101/112

Claims 28-31 stand rejected because the claimed invention allegedly is not supported by either a specific and substantial asserted utility or a well-established utility. Applicant respectfully disagrees.

The claims as amended are drawn to transgenic mouse whose genome comprises a heterozygous disruption in a serine protease gene comprising SEQ ID NO:1 (epithin), the mating of such mice results in embryonic lethality of the homozygous embryos.

According to 35 U.S.C. § 101, “[w]hoever invents . . . any new and useful . . . composition of matter may obtain a patent therefore. . . .”

Under the Patent Office’s Utility Requirement Guidelines:

If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the

invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

...

If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a “specific and substantial utility”) and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

(emphasis added)(MPEP § 2107, II (A)(3); II (B)(1)). Thus, according to Patent Office guidelines, a rejection for lack of utility may not be imposed where an invention has either a well-established utility or is useful for any particular practical purpose. The present invention satisfies either standard.

The present invention has a well-established utility since a person of ordinary skill in the art “would immediately appreciate why” knockout mice are useful. As a general principle, any knockout mouse has the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse. The sequencing of the human genome has produced countless genes whose function has yet to be determined. According to the National Institute of Health, knockout mice represent a critical tool in studying gene function:

Over the past century, the mouse has developed into the premier mammalian model system for genetic research. Scientists from a wide range of biomedical fields have gravitated to the mouse because of its close genetic and physiological similarities to humans, as well as the ease with which its genome can be manipulated and analyzed.

...

In recent decades, researchers have utilized an array of innovative genetic technologies to produce custom-made mouse models for a wide array of specific diseases, as well as to study the function of targeted genes. One of the most important advances has been the ability to create transgenic mice, in which a new gene is inserted into the animal's germline. Even more powerful approaches, dependent on homologous recombination, have permitted the development of tools to "knock out" genes, which involves replacing existing genes with altered versions; or to "knock in" genes, which involves altering a mouse gene in its natural location. To

preserve these extremely valuable strains of mice and to assist in the propagation of strains with poor reproduction, researchers have taken advantage of state-of-the-art reproductive technologies, including cryopreservation of embryos, in vitro fertilization and ovary transplantation.

(<http://www.genome.gov/pfv.cfm?pageid=10005834>) (emphasis added). Thus, the knockout mouse has been accepted by the NIH as the premier model for determining gene function, a utility that is specific, substantial and credible.

Commercial use and acceptance is one important indication that the utility of an invention has been recognized by one of skill in the art (“A patent system must be related to the world of commerce rather than to the realm of philosophy.” *Brenner v Manson*, 383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966)). Commercial use of the knockout mice produced by Assignee Deltagen has been clearly established. Three of the largest pharmaceutical companies in the world, Merck, Pfizer and GSK, have ordered the presently claimed transgenic mouse. This commercial acceptance more than satisfies the practical utility requirement of section 101.

Transgenic mice may be appropriately compared to other research tools, with respect to which the Patent Office has commented:

Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact “useful” in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as “research tool,” “intermediate” or “for research purposes” are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

(MPEP § 2107.01, I). As with gas chromatographs, screening assays and nucleotide sequencing techniques, knockout mice have a clear, specific and unquestionable utility (e.g., they are useful in analyzing gene function).

Applicant submits that since one of ordinary skill in the art would immediately recognize the utility of a knockout mouse in studying gene function, a utility which is specific, substantial and credible, the invention has a well-established utility, thus satisfying the utility requirement of section 101. On this basis alone, withdrawal of the rejection with respect to the present invention is warranted, and respectfully requested.

In addition, the present invention has a practical utility: study of embryogenesis. This utility has been recognized by those skilled in the art. For example, Nebigil et al. (Proc Natl Acad Sci U S A. (2000) 97(17):9508-13) report, based on studies of the knockout mouse, that the serotonin 2B receptor is required for heart development:

Several lines of evidence suggest that the serotonin (5-hydroxytryptamine, 5-HT) regulates cardiovascular functions during embryogenesis and adulthood. 5-HT binds to numerous cognate receptors to initiate its biological effects. However, none of the 5-HT receptor disruptions in mice have yet resulted in embryonic defects. Here we show that 5-HT(2B) receptor is an important regulator of cardiac development. We found that inactivation of 5-HT(2B) gene leads to embryonic and neonatal death caused by heart defects. 5-HT(2B) mutant embryos exhibit a lack of trabeculae in the heart and a specific reduction in the expression levels of a tyrosine kinase receptor, ErbB-2, leading to midgestation lethality. These in vivo data suggest that the Gq-coupled receptor 5-HT(2B) uses the signaling pathway of tyrosine kinase receptor ErbB-2 for cardiac differentiation. All surviving newborn mice display a severe ventricular hypoplasia caused by impaired proliferative capacity of myocytes. In adult mutant mice, cardiac histopathological changes including myocyte disarray and ventricular dilation were consistently observed. Our results constitute genetic evidence that 5-HT via 5-HT(2B) receptor regulates differentiation and proliferation of developing and adult heart. This mutation provides a genetic model for cardiopathy and should facilitate studies of both the pathogenesis and therapy of cardiac disorders in humans.

(abstract)(emphasis added). In another example, Kojima (Int J Hematol. (2002) 76 Suppl 2:36-9), studied knockout mice which also demonstrated embryonic lethality:

The blood coagulation system is a complicated cascade of reactions and feedback regulations that executes a rapid response to vascular injury, yet avoids occlusion of the vessel. There are several key components of this system in the regulation of blood clot propagation, such as antithrombin (AT), tissue factor pathway inhibitor (TFPI), thrombomodulin (TM) and protein C (PC), of which defect causes

thromboembolic diseases. In recent years, targeted gene disruption technique by homologous recombination has been introduced to investigate the physiological roles of those natural anticoagulant molecules, not only in thrombogenesis but also in embryogenesis. We have studied the natural anticoagulation system in a decade, and recently established AT knockout mice as well as ryudocan (syndecan-4) knockout mice. Ryudocan is a cell surface heparan sulfate proteoglycan, which bears heparin-like glycosaminoglycan (heparan sulfate) chains, originally cloned from rat microvascular endothelial cells. We have demonstrated that ryudocan deficiency impairs the control of coagulation in fetal vessels of the placenta in mice. We have also reported that complete antithrombin deficiency in mice results in embryonic lethality, with severe fibrin deposition in the myocardium and the liver, accompanied with extensive subcutaneous hemorrhage. In this presentation, recent advances in understanding roles of natural anticoagulant molecules through the researches of targeted gene-knockout mice, including our experiences in antithrombin deficient mice and ryudocan deficient mice, will be discussed.

(abstract)(emphasis added). The serotonin 2B receptor gene knockout, the 5-HT receptor knockout and the claimed epithin gene knockout all demonstrated embryonic lethality. Each of these mice is useful in studying the role of the gene in embryogenesis. It is clear that those of skill in the art, including Nebigil and Kojima, would recognize the use and importance of the claimed invention.

It is Applicant's position that the claimed invention has both a well-established utility in the study of gene function as well as a practical specific utility in the study of embryogenesis, either of which satisfies the utility requirement. Withdrawal is respectfully requested.

Rejections under 35 U.S.C. § 112, 1st paragraph

The claims have also been rejected since the claimed invention allegedly lacks utility; it fails to comply with the enablement requirement. Applicants respectfully traverse the rejection. For reasons set forth above, the claimed invention satisfies the utility requirement of section 101, and therefore one of skill in the art would know how to use the invention.

Claims 21-25 are also rejected on the ground that producing a transgenic with a phenotype is unpredictable. The specification teaches how to make the claimed invention. A disruption in another part of the gene resulting in non-lethal embryonic

phenotype is outside of the scope of the present claims. The specification need not teach that which is not claimed.

The Examiner also argues that there is no genotyping confirming the homozygous disruption or whether the phenotype was a result of random integration. The specification states that homozygous mice were identified as embryos (Example 1). This statement must be taken as factually true unless the Examiner has an objective basis for questioning the truth of the statement.

The Examiner argues that the claims read on breeding a mouse with the same or different disruption. The specification teaches how to generate a heterozygous mouse and to breed the mouse to generate a homozygous embryo with a developmental lethality. The specification need not teach each and every position on the gene where such disruption may be introduced. If a different disruption or breeding of heterozygous mice with different disruptions result in a homozygous mouse which does not demonstrate an embryonic lethality, then it is outside the scope of the claims.

Enablement must be assessed in light of the claimed invention. Applicant submits that the specification enables the invention as claimed. Withdrawal of the rejection is respectfully requested.

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-386.

Respectfully submitted,

Date: September 20, 2004

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